von Willebrand Disease and Other Inherited Bleeding Disorders In Women with Diagnosed Menorrhagia

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Bleeding disorders, especially von Willebrand Disease, are not uncommon in women with menorrhagia.

ABSTRACT

Objective: This study sought to estimate the prevalence of von Willebrand Disease and other bleeding disorders in women with and without diagnosed menorrhagia.

Methods: Women with menorrhagia were identified among members of a health maintenance organization in the southeastern United States through a computer search for appropriate ICD-9 codes. A random sample of members with no such code was selected as controls. The study included 121 women with menorrhagia and 123 controls. Subjects were interviewed in-person and blood was drawn for coagulation testing. Laboratory results for menorrhagia cases were compared to controls using race and blood type specific ranges developed from the control group. A test was considered abnormal if it exceeded two standard deviations below the control mean.

Results: Bleeding disorders (von Willebrand Disease, factor deficiency, or a platelet abnormality) were diagnosed in 10.7% of menorrhagia cases and 3.2% of controls (P=0.02). von Willebrand Disease was present in 8 menorrhagia cases (6.6%) and in one control (0.8%) (P=0.02); separate analyses by race revealed a von Willebrand Disease prevalence of 15.9% among white and 1.4% among black menorrhagia cases (P= 0.01). Women with a bleeding disorder did not differ significantly from controls in other symptoms of bleeding.

Conclusions: The prevalence of inherited bleeding disorders among white women with menorrhagia was substantial, consistent with European data published recently. For unknown reasons, the prevalence of von Willebrand Disease was lower among black women. These findings indicate the importance of considering inherited bleeding disorders as a cause of menorrhagia.

INTRODUCTION

According to medical insurance claims, about 5% of women seek medical attention for menorrhagia.[1] Objectively, menorrhagia is defined as menstrual blood loss exceeding 80 ml per menstruation.[2,3] However, the diagnosis often is made subjectively by patient self-report of excessively heavy menstrual bleeding. Menorrhagia may result from gynecologic, systemic, or iatrogenic causes.[4] However, for about 50% of women with menorrhagia, an underlying cause is not identified.[5] Menorrhagia affects a woman's quality of life adversely. For example, women experiencing menorrhagia often complain that their periods control their lives and limit their daily activities.[6] Menorrhagia also can cause anemia and many women with chronic menorrhagia eventually are surgically treated by endometrial ablation or hysterectomy.[7]

Menorrhagia is a common symptom of von Willebrand Disease.[8,9] von Willebrand Disease is a genetic condition characterized by a reduction in the quantity (type I or type III) or quality (type II) of von Willebrand factor, a protein required for normal blood clotting.[10] Type I is the mildest and most common form of the disease and may affect 1-2% of the general population.[11,12] Recent studies from England and Sweden identified mild inherited bleeding disorders, most of which were von Willebrand Disease, in 17 and 37% of women with menorrhagia, respectively.[13,14] The 17% prevalence was obtained from a study in which menorrhagia was classified by self-report,[13] whereas the 37% prevalence was obtained in a study in which menorrhagia was determined from measurements of blood loss.[14] We conducted a study to assess the prevalence of von Willebrand Disease and other inherited bleeding disorders among women with and without a diagnosis of menorrhagia identified through a

medical record search of a large health maintenance organization in the southern United States.

MATERIALS AND METHODS

The study population consisted of reproductive-age women (i.e., 18-45) cared for at a single medical group in Atlanta, Georgia during the period between January 1, 1995 and January 1, 1997. The women were all members of the same health maintenance organization (HMO). Two groups of women were included in the study, those with a diagnosis of menorrhagia and controls. Cases included all women who consulted a plan physician during the study period and for whom a diagnosis relating to menorrhagia was recorded in their medical record (ICD-9 codes: 625.9, 626, 626.2, 626.6, 626.9). A random age-stratified (age groupings: 18-21, 22-30, 31-40, 41-45) sample of 500 women who were plan members during the study period who did not have any of the above ICD-9 codes in their medical record was selected as controls.

The physician group sent introductory letters to women selected for the study. The letter explained the purpose of the study and requested participation. A stamped, addressed return postcard was included with the letter. Women were asked to return the postcard to the study office and to indicate whether or not they wish to receive additional information about the study. Women who did not respond to the first letter within four weeks were sent a second letter requesting their participation. Women who did not respond to this second mailing were considered non-respondents. Neither the physician group nor the HMO were aware of the identities of the women who participated in the study.

After obtaining informed consent from the respondents, a reproductive history, a menstrual

history (including symptoms), non-gynecologic symptoms of a bleeding disorder, family history suggestive of a bleeding disorder, treatment history, and activities of daily living were obtained in an in-person interview. Each participant was asked to come to the Centers for Disease Control and Prevention Hemostasis laboratory for a single visit at which time a venous blood sample was obtained. Tests for von Willebrand Disease, clotting factor deficiencies, and platelet disorders were performed to determine the presence of inherited bleeding disorders. Each subject was tested once.

Laboratory Methods

Bleeding time was performed at the time of sampling using a Surgicutt device (International Technidyne, Edison, NJ). Blood was collected into evacuated siliconized glass tubes (Becton Dickinson, Franklin Lakes, NJ) containing 3.2% sodium citrate in a ratio of 1:9 with blood. Platelet-poor plasma was prepared by centrifugation of whole blood at 1,660 x g for 20 minutes at 4°C followed by repeat centrifugation of the separated plasma at 30,900 x g for 20 minutes at 4°C. Samples were stored in polypropylene tubes at -70°C. ABO blood types were identified by Smith-Kline Beecham Laboratories (Tucker, GA).

Factor VIII activity was measured by one-stage assay (Diagnostica Stago, Parsippany, NJ) using silica as activator and partial thromboplastin on an automated analyzer using mechanical end-point determination (STA, Diagnostica Stago). von Willebrand factor antigen was measured by enzyme-linked immunosorbent assay (ELISA) using polyclonal antiserum (Asserachrom von Willebrand factor, Diagnostica Stago, Parsippany, NJ)). Ristocetin cofactor was measured by aggregation of lyophilized normal platelets (BioData Corp., Hatboro, PA) by ristocetin (American Biochemical and

Pharmaceutical Corp., Marlton, NJ) in an optical system (Biodata Corp., Hatboro, PA). Von Willebrand factor "activity" ELISA was performed as described by Murdock et al,[15] using a monoclonal antibody to von Willebrand factor (American Diagnostica, Greenwich, CT). Ristocetin-induced platelet aggregation was assessed in platelet-rich plasma using 1.2 mg/mL and 0.6 mg/mL ristocetin (Biodata Corp., Hatboro, PA). Ristocetin-induced platelet aggregation was expressed as % aggregation.

Reference standards for Factor VIII and von Willebrand factor were lyophilized commercial reference plasmas standardized against the 3rd International Standard for Factor VIII and von Willebrand Factor in Plasma (3rd International Standard). Unitage was verified in house by comparison to 3rd International Standard with the methodology in use for the study. Logarithmic transformation was used for all calculations of Factor VIII, von Willebrand factor antigen, von Willebrand factor activity, and

Factors II, V, VII, IX, X, XI, and XII were measured using appropriate deficient plasmas (Diagnostica Stago, Parsippany, NJ) on an automated analyzer (STA, Diagnostica Stago). Platelet function was assessed using the subject's platelet rich plasma in an optical aggregometer (Biodata Corp. Hatboro, PA). Agonists used and their final concentrations were 10, 5, and 2 µM ADP, 0.5 mg/mL arachidonic acid, 0.19 mg/mL collagen, and 10 µM epinephrine (Biodata Corp., Hatboro, PA).

Blood type and race-specific ranges were calculated for each factor using the control distributions.[16] A result was considered abnormal if it fell two standard deviations below the control

mean.

Study subjects were classified as having von Willebrand Disease if two or more tests of von Willebrand factor antigen, von Willebrand activity, ristocetin cofactor, or ristocetin-induced platelet aggregation were abnormal based upon the control range. Subjects were classified as having a platelet defect if bleeding time was prolonged, aggregation to adenosine diphosphate, collagen, or epinephrine was abnormal with normal aggregation to arachidonic acid, and no use of medications interfering with platelet function was reported. For simplicity of presentation, the rubric inherited bleeding disorder is used to describe subjects with von Willebrand Disease, a platelet deficiency, or a deficiency of Factor VII or Factor XI.

Fisher's exact test for 2X2 tables with mid-P values and 95% confidence intervals (95% CI) were used to compare the prevalences of inherited bleeding disorders between cases and controls.[17,18] Two-tailed values are reported and a finding is considered statistically significant if P is less than or equal to 5%. Ninety-five percent confidence intervals (CI) for odds ratios and population proportions are reported where appropriate.

RESULTS

We identified 580 women with a diagnosis of menorrhagia in our computer search. About one third (30%) of both menorrhagia case and control women returned the postcard expressing either interest in the study or declining participation. Complete enrollment into the study was achieved for 121 menorrhagia cases and 123 controls.

Demographic characteristics were similar in menorrhagia cases and controls (Table 1). The majority of women who participated in the study were black with about one third being white. The mean age both of cases and controls is about 35 years, and the majority of subjects attended college. Slightly less than half of the study population had type O blood. One case and one control reported that a bleeding disorder had been diagnosed by a physician in a first degree relative. On the other hand, about one-third of cases and one-third of controls reported at least one family member was an excessive bleeder. No subject reported a previous personal diagnosis of a bleeding disorder.

The prevalence of inherited bleeding disorders for cases and controls identified by our laboratory testing is presented in Table 2. Eight (6.6%) menorrhagia cases had von Willebrand Disease as compared with one (0.8%) control. Thus, the prevalence odds of von Willebrand Disease was 8.6 times higher among women with menorrhagia than among control women (95% CI 1.3, 194.6, P = 0.02). Two cases had a factor deficiency (one Factor VII and one Factor XI) as opposed to no controls. However, this difference was not statistically significant. The overall prevalence of inherited bleeding disorders identified by our laboratory is approximately 11% and 3% for menorrhagia cases and controls, respectively (Odds Ratio 3.6, 95% CI 1.2, 13.0, P = 0.02).

Among cases of menorrhagia, 7 (16%) of 44 whites (95% CI 6%, 30%) and 1 (1.4%) of 69 blacks (95% CI 0.03%, 8%) had von Willebrand Disease (P = 0.01 whites compared to blacks). Among controls, only one women had von Willebrand Disease and she was black. The overall prevalence of an inherited bleeding disorder, including von Willebrand Disease, factor deficiency, or platelet disorder, was 18% (95% CI 8%, 33%) and 7% (95% CI 2%, 16%), for white and black cases respectively (P

= 0.09 whites compared to blacks). Among controls, the overall prevalence of a bleeding disorder was similarly low for whites and blacks (4.3% and 2.6%, respectively; P = 0.6). None of the 9 subjects of other race had an inherited bleeding disorder.

The laboratory results of the relevant diagnostic tests for the nine subjects with von Willebrand Disease are displayed in Table 3. The average age of women with vWD was 30 (range 20-41), slightly younger than the general study population. Eight of these subjects had low von Willebrand factor activity measured by ELISA and seven had low ristocetin cofactor. One woman with normal activity by ELISA and low ristocetin cofactor had an increased Ristocetin-induced platelet aggregation suggesting a Type II variant of von Willebrand Disease. Five of the nine women with von Willebrand Disease had greater than two abnormal test results.

There was little difference in bleeding characteristics between subjects with and without an inherited bleeding disorder (Table 4). Although frequent bruising and nose bleeds were reported more often by more women with an inherited bleeding disorder compared with those without an inherited bleeding disorder, the numbers are small and these differences are not statistically significant. Nine (52%) of 17 subjects with an inherited bleeding disorder and 123 (54%) of 227 subjects without an inherited bleeding disorder reported none of the six signs of excess bleeding displayed in Table 4. Sixty-five (54%) of 121 menorrhagia cases did not report any other signs of excess bleeding besides menorrhagia.

DISCUSSION

In this study we found laboratory evidence of an inherited bleeding disorder in about 11% of women with menorrhagia compared with about 3% of control women. This difference in cases and controls was due almost entirely to a higher prevalence of von Willebrand Disease among cases. The prevalence of factor deficiencies also was higher among cases than controls, while the prevalence of platelet abnormalities was similar in cases and controls. However, the data for these later two conditions is sparse and therefore these findings are not persuasive. Of interest is the finding that the prevalence of von Willebrand Disease was higher among white women with menorrhagia as compared to black women with menorrhagia.

About one-third of women contacted about the study responded. The response was similar in cases and controls. Regardless, it is possible that, among all the menorrhagia cases contacted, it was the women with the most severe or persistent menorrhagia who participated in the study. This potential selection bias could have the effect of inflating the estimate of the prevalence of inherited bleeding disorders when considering all women with menorrhagia.

Our findings of a high prevalence of von Willebrand Disease and other inherited bleeding disorders in white women with menorrhagia are consistent with those from recent reports of predominantly white women from England and Sweden.[13,14] A major advantage of our study is that it included a control group, whereas the other two did not. However, we relied on the presence of appropriate ICD-9 codes to diagnose menorrhagia rather than actual measurement of blood loss[14] or referral to a gynecologic clinic because of heavy menstrual bleeding.[13] Since the diagnosis of menorrhagia is subjective,[2,19] to the extent that ICD-9 codes are inexact or inaccurate, so is our case

definition. Yet, this inaccuracy would lead to a misclassification of case status that would tend to attenuate a positive association between menorrhagia and the presence of inherited bleeding disorders. On the other hand, it may be true that only women with severe menorrhagia would be assigned the appropriate ICD-9 code, so that our case series would over represent women with severe menstrual bleeding. In any event, our findings considered in conjunction with those from England and Sweden provides persuasive evidence that inherited bleeding disorders are an important cause of menorrhagia.

The diagnosis of von Willebrand Disease is difficult and involves a combination of clinical and laboratory indications.[9] Our classification of von Willebrand Disease relied solely on laboratory testing of a single sample and was somewhat stringent in that at least two abnormal test results were required. Several women with menorrhagia in our study had one abnormal test or two borderline tests. We believe that some of these women would have been identified as having von Willebrand Disease in a setting in which a more thorough clinical evaluation and repeat testing was done. Thus, our strict requirements for the laboratory diagnosis of von Willebrand Disease also would tend to provide a low estimate of the prevalence of inherited bleeding disorder among women with menorrhagia.

The racial difference in the prevalence of von Willebrand Disease in our study is intriguing. The obvious interpretation is that the genetic defect(s) that cause von Willebrand Disease are less common among people of African descent than they are among women of European descent. An alternate explanation is a higher prevalence of another cause of menorrhagia among black women compared with white women. Uterine leiomyomas are a cause of excessive menstrual bleeding and these tumors are more common among blacks.[20] However, self-reported uterine leiomoyomas did not differ for black

and white women and, when we excluded subjects who reported a diagnosis of uterine leiomyomas, the higher prevalence of inherited bleeding disorders among whites remained. The use of race-specific control ranges for the laboratory tests for von Willebrand Disease almost certainly does not explain the lower prevalence of von Willebrand Disease among blacks. Our black control subjects, consistent with other research,[21-23] had higher levels of von Willebrand factor antigen, von Willebrand factor activity, and Factor VIII than did white control women. Thus, the use of race-specific references raised the lower threshold at which a test was considered abnormal for black women with menorrhagia. The black woman with menorrhagia and von Willebrand Disease would not have been classified as having von Willebrand Disease had she been white. Finally, it may be true that the diagnosis of menorrhagia is made differently for whites and blacks and that this difference accounts for the difference in the prevalence of inherited bleeding disorders between them in our study. It would require a study with a more objective case definition than that used in our study to distinguish between this explanation and other explanations. Regardless, before we would attach any biologic significance to our finding of a lower prevalence of von Willebrand Disease among black women with menorrhagia compared with whites, we would like to see the finding replicated in a study with a more objective assessment of menorrhagia.

The similarity in the bleeding characteristics in women with inherited bleeding disorders and those without is striking. However, not too much can be made of these findings since our study subjects were relatively young and therefore for the most part, had not been challenged by surgery or trauma. Trauma is the event most predictive of a inherited bleeding disorder.[24] Only easy bruising was

reported commonly among our study subjects and, although its prevalence was higher among those with a bleeding disorder compared to those without, the differences are not statistically significant. Others have reported that menorrhagia is the dominant symptom of an inherited bleeding disorder in women. Kadir, *et al*[13] found that the majority of their subjects with inherited bleeding disorders had no more than two additional symptoms of bleeding in addition to menorrhagia. Only 19% reported easy bruising along with menorrhagia. These observations underline the importance of considering idiopathic menorrhagia as an indication of an underlying inherited bleeding disorder.

The failure to diagnosis an underlying inherited bleeding disorder in a woman with menorrhagia can have important, and dire, implications for her health. Many women with unexplained menorrhagia undergo surgery to correct the problem. However, menorrhagia associated with von Willebrand Disease can be treated effectively with desmopressin nasal spray,[25] improving that woman's quality of life and preventing unnecessary surgical interventions. Furthermore, unanticipated and excessive bleeding during child birth and at surgery can be avoided with prophylactic treatment. This study, along with those of Kadir and Edlund, emphasize the importance that gynecologists consider inherited bleeding disorders as a common cause of unexplained menorrhagia. All of the women in our study whom we diagnosed with von Willebrand disease had low von Willebrand factor activity or ristocetin cofactor (six of the nine were low for both). Based upon these results, it is tempting to recommend that diagnosis be based upon those two tests, easily ordered by the gynecologist. However, the diagnosis of von Willebrand Disease remains controversial. Current recommendations by the Society of Thrombosis and Haemostasis for diagnosis of von Willebrand Disease include a panel of tests, the

results of which are subject to interpretation.[26] As menorrhagia is a common complaint and many cases are unexplained, it is not practical to recommend that all such patients be referred for expensive coagulation testing. A screening tool in the form of a short questionnaire or a simple discriminatory laboratory test which would aid the gynecologist in determining which patients could benefit by a full coagulation work-up is needed. Until the time when such a screening tool is available, referral of severe, idiopathic menorrhagia patients to other specialists for testing and diagnosis is warranted.

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Table 1: Selected Characteristics of Cases and Controls

Characteristic*	**Menorrhagia Cases (n=121)**	**Controls (n=123)**
Mean age (range)	35.5 (20-46)	34.3 (19-47)
Race		
White	44 (36.4%)	46 (37.4%)
Black	69 (57.0%)	76 (61.)
Other	8 (6.5%)	1 (0.8%)
Type O blood type	59 (48.8)	55 (44.5)
Education		
< High school	1 (0.8%)	2 (1.6%)
High school graduate	17 (14.1)	25 (20.3%)
Some college	103 (85.1%)	96 (78.1%)
Family history of excessive bleeding	41 (33.9%)	36 (29.3%)
Family history of diagnosed bleeding disorder	1 (0.8%)	1 (0.8%)

*All p-values for differences between cases and controls exceeded 0.02.

Table 2: Inherited Bleeding Disorders among Cases and Controls

Diagnosis	Menorrhagia Cases (n=121)	Controls (n=123)	p-value	Odds Ratio (95% CI)
von Willebrand Disease*	8 (6.6%)	1 (0.8%)	0.02	8.6 (1.3, 194.6)
Factor Deficiencies†	2 (1.6%)	0	0.20	NA (0.3, inf)
Platelet Abnormality	3 (2.5%)	3 (2.4%)	1.0	1.0 (0.20, 6.0)
TOTAL	13 (10.7%)	4 (3.2%)	0.02	3.6 (1.2, 13.0)

BY RACE

	Menorrhagia Cases			Controls		
Diagnosis	**White (n=44)**	**Black (n=69)**	**p**	**White (n=46)**	**Black (n=76)**	**p**
Any Bleeding Disorder‡	8 (18.2%)	5 (7.2%)	0.09	2 (4.3%)	2 (2.6%)	0.6
von Willebrand Disease	7 (15.9%)	1 (1.4)	0.01	0	1 (1.3%)	0.6

*Based upon two or more tests of von Willebrand factor antigen, von Willebrand factor activity, ristocetin cofactor, or ristocetin-induced platelet aggregation two standard deviations below the control range

†One Factor VII deficiency and one Factor XI

‡Includes von Willebrand Disease, factor deficiencies, platelet defects

Table 3: Laboratory Characteristics of Subjects Classified as Having von Willebrand Disease Using Race and ABO Specific Control Ranges

				2 standard deviations below control range (Yes/No)					
Menorrhagia	**Age**	**Race**	**ABO**	**von Willebrand factor Antigen**	**Ristocetin cofactor**	**von Willebrand factor activity**	**Factor VIII**	**Ristocetin-induced platelet aggregation**	**Abnormal Tests**
Yes	20	White	O	Yes	Yes	Yes	Yes	Decreased	5
Yes	29	White	O	No	Yes	No	No	Increased	2
Yes	27	White	O	No	Yes	Yes	No	Normal	2
Yes	41	White	O	No	No	Yes	Yes	Normal	2
Yes	29	White	A	No	Yes	Yes	No	Decreased	3
Yes	26	White	A	No	Yes	Yes	No	Normal	2
Yes	40	White	A	Yes	Yes	Yes	No	Normal	3
Yes	39	Black	A	Yes	No	Yes	Yes	Normal	3
No	22	Black	A	Yes	Yes	Yes	Yes	Normal	4

Table 4: Other Bleeding Symptoms in Subjects with and without a Bleeding Disorder

All Subjects

	Bleeding Disorder			
Bleeding Symptom	**Yes (n=17)**	**No (n=227)**	**p-value**	**Odds Ratio (95% CI)**
Bruising	6 (35.3%)	52 (22.9%)	0.3	1.8 (0.60, 5.2)
Nose bleeds	1 (5.9%)	4 (1.8%)	0.3	3.4 (0.13, 29)
Gum bleeding	0	25 (11.0%)	0.2	0 (0, 1.7)
Postoperative Bleeding†	0	9 (5.5%)	0.5	0 (0, 6.0)
Bleeding after dental surgery†	1 (6.7%)	15 (7.9%)	0.9	0.9 (0.04, 5.3)
Postpartum bleeding†	1 (16.7%)	26 (18.6)	0.7	0.5 (0.06, 3.8)

† Restricted to persons who had a procedure or pregnancy. Derived as % time bleeding following procedure or pregnancy